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(54) Title: A METHOD FOR TREATING RENAL FAILURE

(57) Abstract: Levosimendan or its active metabolite (II), which have been previously suggested for the treatment of congestive heart failure are useful in the treatment of renal failure.

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## A METHOD FOR TREATING RENAL FAILURE

## Technical field

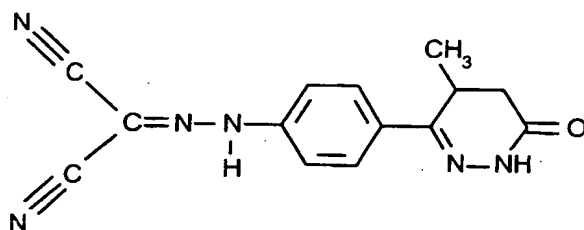
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The present invention relates to a method for the treatment of renal failure by administering levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts, to a mammal in need of such treatment.

10

## Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the method for its preparation is described in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. Levosimendan is represented by the formula:



20

The hemodynamic effects of levosimendan in man are described in Sundberg, S. et al., Am. J. Cardiol., 1995; 75: 1061-1066 and in Lilleberg, J. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S63-S69, 1995. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995. Clinical studies have confirmed the beneficial effects of levosimendan in heart failure patients.

25

Recently it has been found that levosimendan has an active metabolite (R)-N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (II) which is present in human following administration of levosimendan. The effects of (II) are similar to levosimendan. The use of (II) for increasing calcium sensitivity of contractile proteins in the cardiac muscle has been described in WO 99/66932.

30

The mammalian renal system serves primary roles of both in the removal of catabolic waste products from the bloodstream and in the maintenance of fluid and electrolyte balances in the body. Renal failure is characterized by acute or chronic deterioration of kidney function. Renal failure is a life-threatening condition in which the build-up of catabolites and other toxins, and/or the development of significant imbalances in electrolytes or fluids, may lead to the failure of other major organ systems and death. Dialysis and kidney transplantation can be used as treatments, but these procedures can have serious complications.

Thus, there is a need for additional options to the presently available treatments for renal failure.

#### Summary of the invention

It has now been found that levosimendan or its active metabolite (II) or any of the pharmaceutically acceptable salts thereof are useful in the treatment of renal failure.

Therefore, the present invention provides the use of levosimendan or its active metabolite (II) or any of their pharmaceutically acceptable salts in the manufacture of a medicament for the treatment of renal failure.

The present invention also provides the use of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts in the manufacture of a medicament for reducing mortality in a mammal suffering from renal failure the mortality being associated with the deterioration of kidney function.

The present invention also provides a method for the treatment of renal failure in a mammal, said method comprising administering to a mammal in need thereof an effective amount of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts.

The present invention also provides a method for reducing mortality in a mammal suffering from renal failure the mortality being associated with the deterioration of kidney function, said method comprising administering to a mammal

in need thereof an effective amount of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts.

#### Detailed description

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The method of the invention relates to administering to a subject an amount of levosimendan effective to reduce, inhibit or prevent symptoms of renal failure in a mammal, including man. The method of the invention includes administering to a subject an amount of levosimendan effective to reduce, inhibit or prevent  
10 deterioration of renal function in a mammal, including man. The administration of levosimendan or its active metabolite (II) can be enteral, e.g. oral or rectal; parenteral, e.g. intravenous; or transdermal.

As used herein the term "renal failure" means a disease state or condition  
15 wherein the renal tissues fail to perform their normal functions. Renal failure includes chronic and acute renal failure or dysfunction.

Acute renal failure is broadly defined as a rapid deterioration in renal function sufficient to result in accumulation of nitrogenous wastes in the body. The causes of  
20 such deterioration include renal hypoperfusion, obstructive uropathy, and intrinsic renal disease such as acute glomerulonephritis.

Chronic renal failure is usually caused by renal injuries of a more sustained nature which often lead to progressive destruction of nephron mass. Glomeruloneph-  
25 ritis, tubulointerstitial diseases, diabetic nephropathy and nephrosclerosis are among the most common causes of chronic renal failure. Chronic renal failure can be defined as a progressive, permanent and significant reduction in glomerular filtration rate (GFR) due to a significant and continuing loss of nephrons. The clinical syndrome that results from profound loss of renal function is called uremia.

30

Diagnostic signs of renal failure include lower than normal creatinine clearance; lower than normal free water clearance; higher than normal blood urea and/or nitrogen and/or potassium and/or creatinine levels; altered activity of kidney enzymes such as gamma glutamyl synthetase; altered urine osmolarity or volume;  
35 elevated levels of microalbuminuria or macroalbuminuria; glomerular and arteriolar lesions; tubular dilation; hyperphosphatemia; or need for dialysis.

The inhibition of the renal failure can be evaluated by measuring these parameters in mammals by methods well known in the art, e.g. by measuring creatinine clearance.

5        Renal failure can be divided into several stages starting from mild form followed by moderate and severe forms and processing to so called end stage renal disease. These stages can be identified in a conventional way e.g. by determining the creatinine clearance values for which well-defined ranges are assigned to the different stages of renal insufficiency.

10

The effective amount of levosimendan or its active metabolite (II) to be administered to a subject depends upon the condition to be treated, the route of administration, age, weight and the condition of the patient. In general levosimendan is administered orally to man in daily dose from about 0.1 to 20 mg, preferably from  
15    0.2 to 15 mg, more preferably from 0.5 to 10 mg, given once a day or divided into several doses a day, depending on the age, body weight and condition of the patient. The oral daily dose of the active metabolite (II) in man is generally within the range of 0.05 - 10 mg.

20

Levosimendan can be administered by intravenous infusion using the infusion rate typically from about 0.01 to 10  $\mu\text{g/kg/min}$ , more typically from about 0.02 to 5  $\mu\text{g/kg/min}$ . For the intravenous treatment of renal failure an intravenous bolus of 10 - 200  $\mu\text{g/kg}$  followed by infusion of 0.2 - 3  $\mu\text{g/kg/min}$  may be needed. The active metabolite (II) can be administered intravenously using an infusion rate, which is  
25    from about 0.001 to 1  $\mu\text{g/kg/min}$ , preferably from about 0.005 to 0.5  $\mu\text{g/kg/min}$ .

Levosimendan or its active metabolite (II) is formulated into dosage forms suitable for the treatment of renal failure using the principles known in the art. It is given to a patient as such or preferably in combination with suitable pharmaceutical  
30    excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions whereby the contents of the active compound in the formulation is from about 0.5 to 100 % per weight. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants,  
35    colours, sweeteners, wetting compounds, release controlling components and other ingredients normally used in this field of technology may be also used.

For oral administration in tablet form, suitable carriers and excipients include e.g. lactose, corn starch, magnesium stearate, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include e.g. lactose, corn starch, magnesium stearate and talc. For controlled release oral compositions release controlling components can be used. Typical release controlling components include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats and oils including vegetable solid oils such as hydrogenated soybean oil, hardened castor oil or castor seed oil (sold under trade name Cutina HR), cotton seed oil (sold under the trade names Sterotex or Lubritab) or a mixture thereof; fatty acid esters such as triglycerides of saturated fatty acids or their mixtures e.g. glyceryl tristearates, glyceryl tripalmitates, glyceryl trimyristates, glyceryl tribehenates (sold under the trade name Compritol) and glyceryl palmitostearic acid ester.

Tablets can be prepared by mixing the active ingredient with the carriers and excipients and compressing the powdery mixture into tablets. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatin capsules. Typically a tablet or a capsule comprises from about 0.1 to 10 mg, more typically 0.2 to 5 mg, of levosimendan or its active metabolite (II).

Formulations suitable for intravenous administration such as injection or infusion formulation, comprise sterile isotonic solutions of levosimendan or its active metabolite (II) and vehicle, preferably aqueous solutions. Typically an intravenous infusion solution comprises from about 0.01 to 0.1 mg/ml of levosimendan or its active metabolite (II).

The active ingredient of the invention may be administered periodically, e.g. weekly or biweekly, or daily or several times a day, depending on the patient's needs. The elimination half-life of the active metabolite (II) in man is rather long, about 72 h. Therefore, a periodical treatment, e.g. weekly, may be satisfactory.

Salts of levosimendan or its active metabolite (II) may be prepared by known methods. Pharmaceutically acceptable salts are useful as active medicaments, however, preferred salts are the salts with alkali or alkaline earth metals.

## Examples

### Pharmaceutical example.

5

Hard gelatin capsule size 3

Levosimendan 2.0 mg

Lactose 198 mg

10 The pharmaceutical preparation in the form of a capsule was prepared by mixing levosimendan with lactose and placing the powdery mixture in hard gelatin capsule.

### Experiments

15 In total, 701 heart failure patients from levosimendan trials 3001021b and 3001030 were included into the analysis to determine the effect of levosimendan on mortality in patients with normal or impaired renal function.

20 The study 3001021b compared levosimendan with dobutamine in a double-blind, parallel-group, randomised trial in 203 patients with low-output heart. Treatment with levosimendan (n=103) was started with a loading dose of 24 µg/kg infused over 10 minutes and followed by a continuous infusion of 0.1 µg/kg/min. For patients in whom the cardiac index had not increased by at least 30% compared with the baseline value at 2 hours, the dose was doubled to 0.2 µg/kg/min for levosimendan (n=69). Infusions  
25 were continued for totally 24 hours. Mortality was followed prospectively up to 31 days and retrospectively up to 180 days.

30 The study 3001030 evaluated the safety of levosimendan in patients with left ventricular failure after an acute myocardial infarction. The study was a placebo-controlled, double-blind, parallel-group, randomised, trial in 504 patients. Levosimendan was administered as a 10-minute loading dose followed by a continuous infusion for a total of 6 hours. The following doses were used: 6 µg/kg + 0.1 µg/kg/min (n=103), 12 µg/kg + 0.2 µg/kg/min (n=100), 24 µg/kg + 0.2 µg/kg/min (n=99), 24 µg/kg + 0.4 µg/kg/min (n=100) and similar placebo infusion (n=102). All-cause mortality was  
35 followed prospectively up to 14-days and retrospectively up to 180-days.

The patients combined from the above studies were classified according to their baseline renal function. The formula of Cockcroft and Gault (Lafayette et al, 1997) was used to calculate the creatinine clearance (CLcr) values from the baseline serum creatinine) values as follows:

5

$$\text{for men: } \text{CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{\text{serum creatinine in mg/dl} \times 72}$$

10

$$\text{for women: } \text{CLcr} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{\text{serum creatinine in mg/dl} \times 85}$$

The 180-day mortality in patients with normal renal function and renal impairment is shown in Table 1.

15 Table 1. 180-day mortality in patients with normal or impaired renal function.

Renal function	Mortality in levosimendan groups	Mortality in control groups
Normal (CLcr > 80 ml/min)	15 % (24/156)	24 % (19/80)
Mild impairment (CLcr 50 – 80 ml/min)	18 % (38/206)	35 % (24/68)

The decrease in mortality was highest in patients with impaired renal function, which demonstrates the beneficial effects of levosimendan on impaired renal function.

20

#### References:

Lafayette RA, Perrone RD, Levey AS (1997). Laboratory evaluation of renal function in Diseases of the kidney. Edited by Schrier RW, Gottschalk CW, 6<sup>th</sup> edition, Vol 1, pages  
25 314-319. Little, Brown and Company, Boston New York Toronto London.



## Claims

1. Use of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts in the manufacture of a medicament for the treatment of renal failure.

2. Use of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts in the manufacture of a medicament for reducing mortality in a mammal suffering from renal failure the mortality being associated with the deterioration of kidney function.

3. A method for the treatment of renal failure in a mammal, said method comprising administering to a mammal in need thereof an effective amount of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts.

4. A method for reducing mortality in a mammal suffering from renal failure the mortality being associated with the deterioration of kidney function, said method comprising administering to a mammal in need thereof an effective amount of levosimendan or its metabolite (II) or any of their pharmaceutically acceptable salts.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/FI2004/000002

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/50 A61P13/12

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM-ABS Data, BIOSIS, EMBASE, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE WPI Section Ch, Week 199314 Derwent Publications Ltd., London, GB; Class B03, AN 1993-111711 XP002283338 &amp; JP 04 368328 A (TEIKOKU HORMONE MFG CO LTD) 21 December 1992 (1992-12-21) abstract</p>	1-4
A	<p>EP 0 565 546 A (ORION YHTYMAE OY) 20 October 1993 (1993-10-20) cited in the application the whole document</p> <p style="text-align: center;">----- -/--</p>	1-4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

4 June 2004

Date of mailing of the international search report

29. 06. 2004

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/FI2004/000002

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PAGEL P S ET AL: "PHARMACOLOGY OF LEVOSIMENDAN: A NEW MYOFILAMENT CALCIUM SENSITIZER"</p> <p>CARDIOVASCULAR DRUG REVIEWS, NEVA PRESS, BRANFORD, CT, US, vol. 14, no. 3, 1996, pages 286-316, XP008030915</p> <p>ISSN: 0897-5957</p> <p>the whole document</p>	1-4
A	<p>-----</p> <p>PAGEL P S HETTRICK D A ET AL: "INFLUENCE OF LEVOSIMENDAN PIMOBENDAN, AND MILRINONE ON THE REGIONAL DISTRIBUTION OF CARDIAC OUTPUT IN ANAESTHETIZED DOGS"</p> <p>1996, BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, PAGE(S) 609-615 , XP002901958</p> <p>ISSN: 0007-1188</p> <p>abstract</p> <p>page 611, column 1, paragraph 3</p> <p>-----</p>	1-4

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/FI2004/000002

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 3,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/FI2004/000002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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